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In re application of:	Confirmation No. 8113
Dale B. Schenk et al.	Examiner: Daniel E. Kolker
Application No.: 10/699,517	Technology Center/Art Unit: 1649
Filed: October 31, 2003	APPELLANTS' BRIEF UNDER 37 CFR §41.37
For: PREVENTION AND TREATMENT OF SYNUCLEINOPATHIC DISEASE	

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
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Sir:

Further to the Notice of Appeal mailed October 13, 2008 in the above-referenced application, Appellants submit this Brief on Appeal.

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1. REAL PARTY IN INTEREST

The real parties in interest are Elan Pharma International Ltd. and the Regents of the University of California, the assignees of record.

2. RELATED APPEALS AND INTERFERENCES

This is the second appeal brief filed in the present case. The Examiner reopened prosecution following filing of the first appeal brief. A Board decision in a related case 09/723,765 is potentially relevant to some of the issues discussed under 35 U.S.C. §112, first paragraph.

3. STATUS OF CLAIMS

Claims 41-46, 48, 51-55, 71-76 and 79-84 are pending and appealed. Claims 1-40, 47, 49, 50, 56-70, 77 and 78 have been cancelled.

4. STATUS OF AMENDMENTS

No amendment after final has been filed.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The present claims are generally directed to methods of treating or effecting prophylaxis of Parkinson's disease using an agent that induces an immunogenic response to Aβ, and in some claims, a second immunogenic agent that induces an immunogenic response to alpha synuclein. Aβ forms extracellular aggregates, better known as plaques, the characteristic pathology of Alzheimer's disease. Alpha synuclein forms intracellular aggregates, also known as Lewy bodies, the characteristic pathology of Parkinson's disease. The application provides data that immunization with alpha synuclein generates antibodies to alpha synuclein and thereby reduces aggregates of alpha synuclein in a transgenic animal model of Parkinson's disease (paragraph 170 and Fig. 2). The application also provides data that immunization with Aβ (i.e., the principal peptide associated with Alzheimer's disease), which has previously been demonstrated to generate antibodies to Aβ and thereby reduce aggregates of Aβ in an animal model of Alzheimer's disease, also reduces aggregates of alpha-synuclein (i.e., the principal

pathology associated with Parkinson's disease). This reduction was observed in both a combined animal model of Alzheimer's and Parkinson's disease in which both aggregates of Aβ and alpha-synuclein were present and a model of Parkinson's disease in which aggregates of alpha-synuclein were present without abnormal aggregates of Aβ (specification at paragraph 186 and Figs. 5 and 6). That Aβ immunization can reduce alpha-synuclein deposits even in the absence of accumulation of abnormal deposits of Aβ suggests that the claimed methods are useful on Parkinson's patients lacking concomitant Alzheimer's disease.

Four independent claims are on appeal.

Independent claim 41 is directed to a method of therapeutically treating a patient suffering from Parkinson's disease. Such methods are generally described at paragraphs 51 and 137. The methods comprise administering to the patient an effective regime of an agent that induces an immunogenic response against Aβ. The rationale for administering Aβ against patients with Parkinson's disease is discussed in paragraph 52 and exemplified in paragraph 186. The agent is Aβ or an immunogenic fragment thereof in combination with an adjuvant, or an antibody to Aβ, as described at paragraphs 117-132 and 144-146 of the specification.

Claim 54, which depends from claim 41, specifies that the patient is free of Alzheimer's disease. Claim 81, which also depends from claim 41, specifies that the patient is free of clinical symptoms of a disease characterized by extracellular amyloid deposits. Such patients are described at e.g., paragraph 134 of the specification. The rationale for treating such patients is provided by the example at paragraph 186 as discussed above.

Independent claim 44 is also directed to a method of therapeutically treating a patient suffering from Parkinson's disease. However, claim 44 comprises administering to the patient an effective regime of two agents, as generally described at e.g., paragraphs 51 and 137. One agent induces an immunogenic response against Aβ and is Aβ or an immunogenic fragment thereof or an antibody to Aβ as discussed in connection with claim 41. The other agent induces an immunogenic response against alpha-synuclein. This agent is alpha synuclein or an immunogenic fragment thereof or an antibody to alpha-synuclein, as described at paragraphs 53-116.

Independent claim 71 is directed to a method of prophylactically treating a patient having a known genetic risk of Parkinson's disease. Such methods are described at e.g., paragraph 133 and 137. The method comprises administering to the patient an effective regime of an agent that induces an immunogenic response to Aβ. The agent is Aβ or an immunogenic fragment thereof, or an antibody to Aβ, as described at paragraphs 117-132 of the specification.

Claim 79, which depends from claim 71, specifies that the patient is free of Alzheimer's disease. Claim 80, which depends from claim 79, further specifies that the patient has no risk factors of Alzheimer's disease. Such patients are described at e.g., paragraph 134 of the specification.

Independent claim 74 is also directed to a method of prophylactically treating a patient having a known genetic risk of Parkinson's disease. As in claim 44, claim 77 specifies administering two agents. One agent is Aβ or an immunogenic fragment thereof or an antibody to Aβ. The other agent is alpha-synuclein or an immunogenic fragment thereof or an antibody to alpha-synuclein as described at paragraphs 53-116.

Claim 84, which depends from claim 74, specifies that the patient is free of clinical symptoms of a disease characterized by extracellular amyloid deposits. Such patients are described at e.g., paragraph 134 of the specification.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

6.1 Whether claims 41-46, 48, 51-55, 71-76 and 79-80 lack enablement under 35 U.S.C. §112, first paragraph.

6.2 Whether claims 41, 42, 44, 45, 46, 48, 51-55, 71, 72, 74, 75, 76 and 80-84 are anticipated by Jensen, US 2002/0187157 [Jensen, 2002] or Jensen, US2003/000086938 [Jensen, 2003] under 35 U.S.C. §102(e).

6.3 Whether claims 41, 43-46, 48, 51-55, 71, 73-76, 79-80 and 80-84 would have been obvious under 35 U.S.C. §103(a) over Jensen, 2002 or Jensen, 2003.

7. ARGUMENT

7.1 Claims 41-46, 48, 51-55, 71-76 and 79-80 do not lack enablement under 35 U.S.C. §112, first paragraph.

7.1.1 The Examiner's Rationale

The Examiner's rationale has been variously stated in the final office action of May 13, 2008, the office action of June 6, 2007, and the office action of May 15, 2006. The final office action of May 13, 2008 indicates that the remaining concerns are directed only to prophylactic embodiments (office action at p. 2). However, the rejection is also applied to claims directed to therapeutically treating a patient suffering from Parkinson's disease based on the allegation that such claims encompass treating patients with some pathological characteristics of Parkinson's disease but which have not yet developed detectable symptoms or signs of the disease (office action at pp. 2-3). The underlying allegation for the rejection is that the animal model of Parkinson's disease used in the Examples of the application necessarily develops pathology of Parkinson's disease and is not a valid model for a general human population in which Parkinson's disease may or may not develop. The Examiner further alleges the model does not take into account environmental factors such as toxins that may contribute to development of Parkinson's disease along with genetic risk (office action at pp. 3-4). In the office action of June 6, 2007, the Examiner further alleges that the claims lack enablement for treating persons with no signs, symptoms or risks for Parkinson's disease (office action at pp. 3-5). The Examiner also intimates that the efficacy to side effects ratio is less favorable for prophylaxis than treatment (office action at pp. 5-6). The office action of May 15, 2006 indicates that the rejection is based on prophylaxis encompassing complete prevention (at p. 3, second paragraph).

7.1.2 Appellants' Position: Claims 41-46, 48, 51-55

Appellants begin by addressing the Examiner's allegation in the office action of May 13, 2008 that claims directed to therapeutically treating a patient suffering from Parkinson's disease (i.e., claims 41-46, 48, 51-55) lack enablement because they encompass treating a patient with some pathological characteristics of disease but in which signs and symptoms are not yet

diagnosable. (The office action did not reject claims 81-82 for lack of enablement. In case these claims were inadvertently omitted from the statement of rejection, appellants note that their position below with respect to claims 41-46, 48, and 51-55 also applies to claims 81 and 82).

Even assuming *arguendo* patients with early disease pathology insufficient to give rise to detectable signs or symptoms of disease are considered to be suffering from the disease, there is no apparent reason that such patients could not be treated in the same manner as patients with more advanced disease. It is unclear why treatment when little pathology has developed would be viewed as more demanding than treatment when extensive pathology has developed. It is common knowledge that in most diseases, early treatment is likely to be even more effective than when full-blown pathology has already developed.

Further, assuming *arguendo* that there were some special difficulty about treating patients with early pathology insufficient for detectable signs or symptoms of disease, such would not be detrimental to enablement of claims 41-48, 51-55 and 81-82. Enabling the full scope of a claim does not necessarily require enabling every embodiment within the claim (see *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984) and other cases cited below in connection with the complete prevention issue). An allegation that the claims might encompass a subclass of patients of ill-defined and transient disease status that is particularly difficult to treat, even if correct, would be insufficient to negate enablement of a generic method of treatment claim.

7.1.3 Appellants' Position: Claims 71-76 and 79-80

Appellants now turn to the Examiner's comments regarding methods of prophylactic treatment (claims 71-76, and 79-80). (The office action did not reject claims 83-84 for lack of enablement. In case the lack of rejection was an inadvertent omission, appellants note that their position below with respect to claims 71-76 and 79-80 also applies to claims 83 and 84.) The office action of May 13, 2008 alleges the mouse model of Parkinson's disease used in the specification does not accurately reflect the treated patients in that the mouse model inevitable develops Parkinson's pathology and does not take into account environmental factors such as toxins. In reply, the Examples of the specification show that treatment reduces alpha-synuclein aggregates in a mouse model genetically disposed to develop such aggregates. The

mice used in the study were at least 12 months old (see Table 6) by which time, it can be agreed that the aggregation process of alpha-synuclein was likely already underway. However, the fact that treatment can reduce alpha-synuclein aggregations when the disease process is already underway, makes it more, not less likely that the treatment would be effective at an earlier stage if administered earlier in the development of such aggregations or before any aggregations had formed. As noted above, it is common knowledge that in most diseases, early treatment is likely even more effective than when full-blown pathology has already developed.

That the mouse model may differ from human patients at known genetic risk of disease receiving prophylaxis in that not all such human patients necessarily develop the disease is submitted to be irrelevant. In patients developing the disease, the development of pathology in a mouse model serves as a model of similar pathology in a patient. In patients not developing the disease, no treatment for the disease is needed and it is of no consequence whether the model mimics conditions in these patients.

That there may be factors in human patients not present in mice that either mitigate or exacerbate disease resulting from genetic risk is also submitted to be irrelevant. Regardless of whether disease develops solely as a result of genetic risk factors, or as a combination of a genetic risk factor and other factors, the underlying pathology of alpha-synuclein aggregations still develops. The Examples of the present specification show that the claimed methods can inhibit development of such pathology.

The office action of June 6, 2007 raised several issues relating to treating patients with no signs, symptoms or risks for Parkinson's disease. However, the present claims directed to methods of prophylaxis require the patient to have a known genetic risk of Parkinson's disease. Therefore, this office action's comments directed to alleged difficulties of prophylaxis of patients not having a known genetic risk of Parkinson's disease are not relevant to claims 71-76, 79-80, 83 and 84.

The office action of June 6, 2007 also intimates that the efficacy to side effects ratio is less favorable for prophylaxis than treatment citing Su, *Brain Research* 818, 105-117 (1999) [Su], Schenk, *Nature Reviews* 3, 824-828 (2002) [Schenk] and Hooper, *Cellular Peptidases in Immune Functions and Di*sease (Langer & Ansorge, Eds, Plenum Publishers,

2000) [Hooper] (office action at pp. 5-6). Even if this is true, it is submitted to be an issue for the patient, the treating physician and the FDA rather than the Patent Office. Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. The requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption. *In re Brana*, 51 F.3d 1561, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995).

In any event, the results of Su, cited are not predictive of the extent of side therapeutics in a method of treatment. The purpose of Su's study was to assess toxic effects of Aβ rather than to assess treatment. Consequently, Su administered Aβ at a much higher frequency that would be necessary or desirable in a method of immunotherapy. Specifically, Su administered Aβ twice a day every day. By contrast typically frequencies of administration in the presently claimed methods are at intervals of weeks or months (see specification at p. 139). Thus, Su's study represents a regime of extreme high exposure specifically designed to promote toxic effects. Such a regime could easily be avoided in a treatment method and is not detrimental to enablement.

As to Schenk's report of side effects in 5% of patients, it is respectfully submitted that such a level of side effects is not inconsistent with enablement under *In re Brana*. Moreover, these side effects reported in Schenk were experienced from administering full-length Aβ peptide not from fragments or antibodies (see p. 828, first column, last paragraph).

With respect to Hooper's discussion of a possible neurological role of APP, it is noted that administration of Aβ for about seven months in a transgenic mouse model of Alzheimer's disease had no effect on APP levels (see US 6,787,144, Example III, particularly at col. 27, lines 23-36). Thus, the allegation that prophylactic treatment as claimed would cause insurmountable side effects through depletion of APP is merely speculation.

In summary, the cited references do not suggest a likelihood of intolerable side effects from prophylactic methods, particularly given that the requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption.

The office action of May 15, 2006 raised a further question of law of whether claims to a method of prophylactically treating Parkinson's disease can be enabled without evidence to show that the methods can achieve *complete* prevention of disease. The Examiner acknowledged that the claimed methods can reduce levels of alpha-synuclein deposits [the principal pathology of Parkinson's disease] in a transgenic animal of model of Parkinson's disease or a transgenic animal model of combined Alzheimer's and Parkinson's disease (office action of October 7, 2005 at p. 7, second paragraph). However, the Examiner alleged lack of enablement on the grounds that appellants have not shown the claimed methods can achieve complete prevention of Parkinson's disease (office action of May 15, 2006 at p. 3).

Applicants and the Examiner appear to agree that prophylactically treating includes but does not require complete prevention. Paragraph 137 of the specification discloses that prophylactic treatment can "eliminate, reduce the risk, less the severity or delay the onset of disease" (*see, e.g.*, specification at paragraph 137). The dictionary definitions cited by the Examiner are largely consistent with the definitions in the specification. Further, the Examiner's remark that the claims "*encompass* both preventing and curing Lewy Body disease" (office action of October 7, 2005 at p. 6, second paragraph, emphasis supplied) suggests the Examiner agrees that prophylactically treating includes but does not require complete prevention.

As previously noted, enabling the full scope of a claim does not necessarily require enabling every embodiment within the claim. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984). This principle is applied to a method of treatment by *In re Cortright*, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999). One of the claims at issue in *In re Cortright* was directed to a method of treating baldness. The Board had rejected the claim for lack of enablement on the basis that the specification did not show restoring the user's hair to its original state (*i.e.*, a full head of hair) but only some improved growth characterized as "filling-in some" or "fuzz" (*Id.* 165 F.3d at 1358, 49 USPQ2d at 1467). The Federal Circuit construed the claims as meaning that the claimed method increased the amount of hair grown on the scalp but did not necessarily produce a full head of hair (*Id.* 165 F3d at 1359, USPQ2d at 1468). The Federal Circuit concluded that

the claims, so construed, were enabled, notwithstanding the lack of evidence that complete restoration could be achieved.

The same principle is illustrated in a different technology by *CFMT, Inc. v. Yieldup Int'l Corp,* 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). The patent at issue was directed to a method of cleaning semi-conductor wafers. The available evidence showed that the disclosed method could remove some contaminants, but could not remove all contaminants, nor even achieve removal of contaminants to a commercial standard. The Federal Circuit reversed the district court's holding of lack of enablement.

> In essence the district court set the enablement bar too high. Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected commercially viable embodiment absent a claim limitation to that effect.
>
> In sum, any meaningful "cleaning" would satisfy the claimed goal of "cleaning of semiconductor wafers."
>
> *Id.* 349 F.3d at 1338-1340, 68 USPQ2d at 1944-45.

An unpublished decision of the USPTO Board of Patent Appeals and Interferences is instructive in applying the above Federal Circuit precedents to claims encompassing methods of treatment. *Ex parte Saito,* Appeal No. 2005-1442 (BPAI 2005, nonprecedential opinion) concerned claims directed to methods of introducing a nucleic acid into a subject by transplanting a hair follicle modified to contain the nucleic acid. The claims were rejected by the examiner for lack of enablement because, although the claims were not limited to therapeutic methods, the claims encompassed such methods, and the examiner took the view that undue experimentation would be required to achieve therapeutic levels of gene expression. The Board followed the precedent of *In re Cortright* in reversing the examiner.

> As with the present claims, the claims in *Cortright* encompassed a method of obtaining results that might be difficult to achieve: here, therapeutically effective gene therapy; in *Cortright,* complete restoration of hair growth. However, as in *Cortright,* the present claims do not require that particular result: the present claims require only introducing or delivering a nucleic acid; *Cortright's* claims required only some restoration of hair growth.

> The court in *Cortright* did not dispute the board's conclusion that completely restoring hair growth using Bag Balm® would require undue experimentation [citation omitted]. The court nonetheless concluded that the claimed method was not nonenabled merely because it encompassed one difficult-to-achieve outcome. The same reasoning applies here: the examiner may be correct that achieving clinically useful gene therapy using the claimed method would require undue experimentation, but the claims are not nonenabled merely for encompassing that difficult-to-achieve outcome.
>
> *Ex parte Saito,* Appeal No. 2005-1442, at pp. 6-7.

Here, the present claims 71-76, 83 and 84 include but do not require complete cure or complete prevention. Assuming *arguendo* that the claimed methods cannot completely prevent Parkinson's disease, they would be no different than prophylaxis with many other highly successful drugs. Further, a quick search of the PTO database reveals that the Patent Office has granted thousands of patents to methods of prophylaxis of disease notwithstanding that it is common knowledge that few drugs achieve such lofty goals as complete prevention. In these circumstances, Appellants submit that in the presently claimed methods, as in other patents claiming methods of prophylaxis, the possibility that the methods may not achieve complete prevention is not detrimental to enablement and need not be excluded from the claims.

The Examiner's remarks in the office action of May 15, 2006 attempting to rebut appellants' position do not address the legal issue above.

> Applicant's arguments are not persuasive because applicant's invention does not teach even one circumstance claimed. There are no examples of curing or preventing and no apparent circumstances wherein any animal is cured or the entire pathology of the disease is prevented.
>
> Office action of May 15, 2006 at p. 3, second paragraph.

Appellants have accepted for purposes of this discussion that the examples of the specification, although showing a reduction in alpha-synuclein deposits in a model of Parkinson's disease, achieved less than a complete cure or complete prevention. What is at issue is whether a claim to a method that includes but does not require complete prevention requires such evidence.

For the reasons given above, appellants respectfully submit that such evidence is not required, and that the rejection should be reversed.

7.2 Claims 41, 42, 44, 45, 46, 48, 51-55, 71, 72, 74, 75, 76 and 80-84 Not Anticipated by Jensen, 2002 or Jensen, 2003.

7.2.1 Summary of the References

The two Jensen patent applications are substantially cumulative with one another, and will be treated as one except when citing to specific paragraphs. The Jensen applications are directed to an alleged improvement to earlier work by Schenk (one of the present inventors) in which immunization with Aβ was shown to reduce deposits of Aβ in the brain of a transgenic model of Alzheimer's disease. The work of Schenk is discussed in paragraphs 49 to 53, 252 and 253 of Jensen, 2003. One of the Schenk references referred to by Jensen at col. 4, line 53, WO 99/27944, is a corresponding application to Schenk, US 6,787,144 (reference #C, cited by Examiner on PTO-892, April 7, 2005). It can be seen that this patent discusses immunization with Aβ to treat Alzheimer's disease, and also mentions that other amyloid peptides responsible for other amyloidogenic diseases can likewise be used in treating the respective disease with each peptide is associated.

> The same or analogous principles determine production of therapeutic agents for treatment of other amyloidogenic diseases. In general, the agents noted above for use in treatment of Alzheimer's disease can also be used for treatment early onset Alzheimer's disease associated with Down's syndrome. In mad cow disease, prion peptide, active fragments, and analogs, and antibodies to prion peptide are used in place of Aβ peptide, active fragments, analogs and antibodies to Aβ peptide in treatment of Alzheimer's disease. In treatment of multiple myeloma, IgG light chain and analogs and antibodies thereto are used, and so forth in other diseases.
>
> US 6,787,144 at col. 12, lines 4-16.

The alleged improvement of Jensen over Schenk resides in the use of modified forms of Aβ or other amyloidogenic peptides to stimulate a stronger immune response (see paragraphs 53, 55, 85, 183 and 251-260 of Jensen, 2003). The Jensen applications are mainly directed to using modified forms of Aβ for the treatment of Alzheimer's disease. However, like the passage of

Schenk, US 6,787,144 quoted above, Jensen also mentions others amyloidogenic diseases and corresponding peptides in which an analogous strategy can be adapted (see paragraphs 43-46 and 247).

7.2.2 The Examiner's rationale

The Examiner's rationale is set forth in the office actions of October 7, 2005 and May 15, 2006 (the Examiner does not further elaborate in the office actions of June 6, 2007 and May 13, 2008). In brief, the Examiner' points to separate sections of the Jensen applications referring to Parkinson's disease or administration of Aβ peptide, and alleges that the artisan would put these together to arrive at a method of treating Parkinson's disease using Aβ peptide. Additionally, or alternatively the Examiner alleges anticipation from disclosure of using Aβ to treat or prevent genera of diseases that include Parkinson's disease within their scope.

7.2.3 The Cited Art Distinguished: Claims 41, 42, 44, 45, 46, 48, 51-55, 71, 72, 74, 75, 76 and 80-84.

In appellants' submission, the Jensen applications do not clearly disclose that Aβ peptide be administered to treat Parkinson's disease. Jensen is mainly directed to administration of Aβ for the treatment of Alzheimer's disease. Jensen also mentions other "Alzheimer-like" diseases, including Parkinson's, Huntington's and prion-related diseases (*see* paragraph 247). However, Jensen does not disclose that the very same treatment for Alzheimer's disease (namely administration of Aβ) should also be given to patients suffering from or at known genetic risk of Parkinson's disease. In fact, Jensen does not refer to administration of Aβ and Parkinson's disease in the same sentence or even the same paragraph. Insofar as one can determine what Jensen is proposing, it would appear more likely he is proposing that amyloidogenic diseases principally associated with peptides other than Aβ be treated not with Aβ, the major peptide associated with Alzheimer's disease, but with whatever peptide plays a comparable role in the disease in question.

In the office action of May 15, 2008, the Examiner alleges that appellant has not identified any support for appellants' proposed interpretation of Jensen. The Examiner also alleges, presumably in favor of an alternative construction of Jensen in which Jensen does

disclose administration of Aβ to Parkinson's patients, that the skilled person would understand the value of using Aβ to treat Parkinson's disease in view of comments by Primavera et al., *J. Alzheimer's Dis.* 1, 183-193 (1999) that deposits of Aβ are found in some Alzheimer's patients.

Appellants respectfully submit that their interpretation of Jensen is in fact more consistent with Jensen's disclosure and what Jensen believes is his own contribution over the art. As discussed above, Jensen believes his contribution over earlier work by Schenk lies in providing modified forms of Aβ and other amyloidogenic peptides that induce enhanced immune responses. Most of the specification is devoted to producing modified forms of Aβ and the examples are devoted to administering modified forms of Aβ to a transgenic animal of Alzheimer's disease. The listing of alternative amyloidogenic peptides and amyloidogenic diseases can thus be understood as an indication that the strategy exemplified for Aβ (i.e., making a modified form and immunizing in a model of Alzheimer's disease) can be extended to other amyloidogenic peptides and their respective diseases. There is no reason to credit Jensen with a second insight of administering Aβ to treat Parkinson's disease when he does not exemplify such a strategy, theorize why such a strategy would work or even describe administering Aβ and treatment of Parkinson's disease in the same sentence or paragraph.

Insofar as Primavera is relied on by the Examiner to support an alternative interpretation of Jensen, appellants submit such reliance is both procedurally and substantively incorrect. Reliance is procedurally incorrect because Primavera is not included in the statement of rejection but is merely mentioned as art that is being made of record but "not relied on." Reliance on Primavera is also improper because Primavera appears to be asserted in a theory of obviousness (i.e., the skilled person would have been motivated to administer Aβ to Parkinson's patients because of Primavera's teaching that some such patients have deposits of Aβ). If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not §102, anticipation but §103, obviousness. *Scripps Clinic & Research Foundation v. Genentech,* 927 F 2d 1565, 1577 (Fed. Cir. 1991); 18 USPQ2d 1001, 1010. Finally, the notion that Primavera does teach the skilled person the value of administering Aβ to treat Parkinson's disease is not an accurate reflection of Primavera's teaching. Primavera observes that Aβ deposits are present in Parkinson's disease (as well as

some other diseases besides Alzheimer's). However, Primavera does not translate this into any plan to treat such patients. On the contrary, Primavera concludes only that further investigation is needed to "better understand the causes and consequences of this pathology" (at p. 190, second column, last paragraph). Thus, the Examiner's allegation that the artisan would understand from Primavera the value of treating Parkinson's disease with Aβ goes well beyond Primavera's teaching.

The Examiner cites several sections of Jensen (office action of October 7, 2005 at pp. 8-9) for the proposition that Jensen discloses administration of Aβ to treat or prevent a genus of diseases that includes Parkinson's disease. For example, the Examiner relies particularly on a sentence in the Background saying that Parkinson's disease is an amyloid associated disease. It is not disputed that the Jensen publications so characterize Parkinson's disease. However, amyloid associated diseases, as the term is used in the Jensen publications, form a broad genus of diseases including Alzheimer's, Parkinson's disease and many others. What is at issue is how the Jensen publications propose to treat Parkinson's disease. This sentence in the background does not address this issue.

The Examiner also points to claims 34 and 20 of US 2002/0187157 (office action of October 7, 2005 at p. 9). Claim 34 is directed to a method of treating or preventing a genus of diseases characterized by amyloid deposits. Claim 20, from which claim 34 depends, specifies a Markush group of about fifty peptides, one of which is Aβ. In combination, claims 34 and 202 are directed to treating a broad genus of diseases with a Markush group of fifty or so agents. Such a genus probably includes over a thousand potential combinations of diseases and agents and does not teach the specific combination of Parkinson's disease and Aβ.

Description of genus having so many potential combinations none of which is individually described does not compensate for the ambiguities throughout the Jensen applications. Although the Jensen applications mention Aβ and Parkinson's disease separately, they are never discussed in the same sentence or paragraph or otherwise in a way that clearly conveyed intent to treat Parkinson's disease with Aβ. A description of a broad genus is insufficient to provide written description of individual members within that genus. *In re Ruschig*, 379 F.2d 990, 995 (CCPA 1967), 154 USPQ 118, 123. "Not having been specifically

named or mentioned in any manner, one is left to select from the myriads of possibilities encompassed by the broad disclosure with no guide indicating or directing that this particular compound should be made rather than any of the many others which could also be made."

A similar analysis applies to claim 27 of US 2003/0086938 referred to by the Examiner at p. 9 of the office action of October 7, 2005. This claim is directed to a method of treating or preventing a genus of Alzheimer's disease or other disease and conditions characterized by Aβ deposits by downregulating Aβ or APP. Assuming *arguendo* that some patients with Parkinson's disease also have deposits of Aβ and thus constitute a subset of the specified genus, and that methods of downregulating Aβ include administration of Aβ, the claim still provides no specific disclosure of the combination of treating Parkinson's disease with Aβ.

To argue that a claim to a genus inherently discloses all species is "wholly meritless whether considered under section 102(b) or under 103." *Corning Glass Works v. Sumito Electric,* 868 F.2d 1251, 1262 (Fed. Cir. 1989), 9 USPQ2d 1962, 1970. To anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity" to constitute an anticipation under the statue. What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. MPEP § 2131.03. The criticality of a claimed subgenus turns on whether the claim is an advance over prior products and processes previously known and sufficiently distinctive to warrant a patent monopoly. There must be a distinctive physical, here a chemical, discovery. *California Research Lab. v. Ladd,* 356 F.2d 813, 820 (DC Circuit 1966), 148 USPQ 404, 410. Here, the prior art genus is directed to treating or preventing Alzheimer's disease or other disease characterized by deposits of Aβ. Virtually anyone is potentially susceptible to Alzheimer's disease if they live long enough and could thus could be treated to prevent Alzheimer's disease. The present claims encompass only a relatively narrow species of this genus, that is, patients suffering from or at known genetic risk of Parkinson's disease. Moreover, treatment of the claimed class of patients is associated with a result not shared by the broader genus. That is, in treatment of claimed class of patients, the

agent is active not only against Aβ deposits that characterize the entire genus, but against synuclein deposits that characterize the claimed class of patients (see specification at paragraph 186 and Figs. 5 and 6). There is nothing in the art to indicate that this result was expected before the effective filing date of the invention.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a prima facie case based upon the prior art (*In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984)). If the evidence is in "equipoise," an inventor is "entitled to a patent." *In re Oetiker,* 977 F.2d 1443 (Fed. Cir. 1992), 24 USPQ2d 1443, 1447 (Plager, J., concurring). A "prior art reference—in order to anticipate under 35 U.S.C. 102--must not only disclose all element of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net Moneyin, Inc. v. Verisign, Inc,* 545 F.3d 1359, 1369 (Fed. Cir. 2008), 88 USPQ2d 1751, at 1758-1759. In other words, "the [prior art] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."). *Id.* 545 F.3d at 1758, 88 USPQ2d at 1369 (emphasis in the original).

Here, the cited reference refers separately to Aβ and Parkinson's disease but never in the same sentence or paragraph or otherwise in a manner that clearly conveys an intent to administer Aβ for the treatment of Parkinson's disease. As discussed above, it is in fact unlikely that this was what Jensen intended. However, insofar as there is doubt on this issue, the doubt should inure to the benefit of appellants given that the burden of proof rests with the Patent Office.

The case of *Impax v. Aventis,* 545 F.3d 1312 (Fed. Cir. 2008), 88 USPQ2d 1381 is also instructive. This case concerned claims to a method of treating ALS with riluzole. A prior art reference disclosed riluzole along with many other compounds and ALS along with many other diseases. The court found that mere mention of riluzole and treatment of ALS in the same document was not sufficient to provide an enabling and therefore anticipating disclosure of a method of treating ALS with riluzole (at p. 1384). Although the rationale for the decision was articulated in terms of lack of enablement of the prior art reference rather than a simple failure to

directly relate elements as in the claims at issue, the case illustrates a larger principle that a prior art reference discussing many different compounds and many different diseases cannot simply be assumed to anticipate every permutation of compound and disease.

7.2.4 Additional Distinctions: Claims 54, 55, and 81-84.

The Board is also requested to consider the patentability of claims 54, 55 and 81-84 directed to methods of treatment or prophylaxis of patients free of Alzheimer's disease or patients free of clinical symptoms of amyloidogenic diseases characterized by extracellular amyloidogenic deposits. The cited Jensen applications provided no specific disclosure connecting treatment with Aβ or antibodies thereto with such patients free of Alzheimer's disease or free of clinical symptoms of diseases characterized by extracellular amyloid deposits. Although the Jensen applications might evidence intent to treat Parkinson's patients, they do not distinguish between Parkinson's patients with or without concurrent Alzheimer's disease. Thus, the Jensen publications provide no specific disclosure of the classes of patients to which claims 54, 55 and 81-84 are directed, much less a clear intent to treat such patients with Aβ or an antibody thereto.

In the office action of May 15, 2006, the Examiner addresses the above position but in the context of the rejection under 35 U.S.C. 103(a) rather than in the context of 35 U.S.C. 102(e) in which the above distinctions were raised. In any event, the Examiner's position is that Jensen discloses prevention of Alzheimer's disease and that the only way to prevent Alzheimer's disease is to administer it to patients who do not have Alzheimer's disease. Presumably, the Examiner's point is that such a genus would include some patients suffering from Parkinson's disease (as required by claims 54, 55, 81 and 82) and some patients at known genetic risk of Parkinson's diseases (as required by claims 83 and 84). This position raises a similar issue to that previously discussed. Disclosure of a genus does not necessarily anticipate or render obvious a species when that species is not specifically enumerated by the reference, particularly when that the species is a relatively small part of the genus disclosed in the reference and associated with an unexpected result. Here, the genus of the cited art is large in that virtually anyone who does not suffer from Alzheimer's disease could be treated to prevent Alzheimer's

disease from developing in the future. The claims at issue encompass only a narrow species of that genus, namely patients suffering from Parkinson's disease or a known genetic risk thereof. Moreover, this species is associated with an unexpected result: immunization with Aβ reduces alpha-synuclein deposits even in the absence of abnormal Aβ deposits (specification at paragraph 186 and Figs. 5 and 6). Although Aβ has been previously shown to reduce deposits of Aβ (see, e.g., US 6,787,144), there was no reason to expect it would reduce the deposits of a different protein alpha-synuclein particularly in patients lacking abnormal deposits of Aβ. Because claims 54, 55 and 81-84 encompass only a small species of the prior art genus of subjects not already having Alzheimer's or other amyloidogenic disease who can be subject to prophylaxis for Alzheimer's disease, and this species is associated with an unexpected result, the present claims are not anticipated or rendered obvious by the Jensen applications.

7.2.5 Additional Distinctions for Claims 44 and 74.

Claims 44 and 74 are further distinguished in that the Jensen applications do not provide specific disclosure of methods in which a combination of Aβ or antibody thereto and alpha-synuclein or an antibody thereto is administered. Although the Jensen publications may generally refer to using at least one amyloidogenic polypeptide or subsequence thereof, the publications list many examples of such polypeptides, and do not disclose the specific combination of Aβ and alpha-synuclein. The Examiner has not addressed these distinctions to date.

7.3 Claims 41, 43-46, 48, 51-55, 71, 73-76, 79-80 and 80-84 Not Obvious Over Jensen, 2002 or Jensen, 2003.

The rejection was originally applied on the basis that Jensen teaches all elements of the above claims except the administration of antibodies instead of immunogenic peptides. The Examiner took the view that administration of antibodies would have been obvious in view of the goal of vaccination with peptides being to generate antibodies (office action of October 7, 2005 at p. 10, last paragraph). In reply, appellants disagree that Jensen teaches all elements of

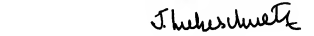
the above claims except the administration of antibodies, for the reasons discussed in connection with the anticipation rejection. Thus, the further issue of disclosure of antibodies is moot.

In the office action of May 15, 2006 (and subsequent office actions), the Examiner does not further address the issue of disclosure of antibodies but instead refers to appellants' remark on the separate patentability of claims 54, 55 and 81-84 which were made with respect to the rejection under 35 U.S.C. 102(e). The tenor of the Examiner's remarks ("Jensen clearly contemplates the limitations of said claims," office action of May 15, 2006 at p. 4, second paragraph) suggests that the Examiner's remarks were in reference to the rejection under 35 U.S.C. 102(e) rather than a new ground of obviousness rejection. Thus, these remarks have been addressed above, and appellants do not further address them here.

8. CONCLUSION

For these reasons, it is respectfully submitted that the rejections should be reversed.

Respectfully submitted,



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9. CLAIMS APPENDIX

41. A method of therapeutically treating a patient suffering from Parkinson's disease, the method comprising

administering to the patient an effective regime of an agent that induces an immunogenic response against Aβ in the patient and thereby therapeutically treating the disease;

wherein the agent is (i) Aβ or an immunogenic fragment thereof and the agent is linked to a carrier that helps elicit an immune response to the agent or is administered with an adjuvant that augments an immune response to the agent, or is (ii) an antibody to Aβ.

42. The method of claim 41, wherein the agent is Aβ or an immunogenic fragment thereof.

43. The method of claim 41, wherein the agent is an antibody to Aβ.

44. A method of therapeutically treating a patient suffering from Parkinson's disease, comprising

administering to the patient an effective regime of an agent that induces an immunogenic response against alpha-synuclein and an agent that induces an immunogenic response against Aβ in the patient and thereby therapeutically treating the disease;

wherein the agent that induces an immunogenic response against alpha-synuclein is alpha synuclein or an immunogenic fragment thereof, and the agent is linked to a carrier that helps elicit an immune response to the agent or is administered with an adjuvant that augments an immune response to the agent, or an antibody to alpha synuclein, and the agent that induces an immunogenic response against Aβ is Aβ or an immunogenic fragment thereof, or an antibody to Aβ.

45. The method of claim 41, wherein the agent is administered peripherally.

46. The method of claim 41, wherein the effective regime comprises administering multiple dosages over a period of at least six months.

48. The method of claim 41, wherein the patient has a risk factor for the disease.

51. The method of claim 41, wherein the administering results in improvement in a sign or symptom of Parkinson's disease.

52. The method of claim 41, wherein the administering improves motor characteristics of the patient.

53. The method of claim 41, further comprising monitoring a sign or symptom of Parkinson's disease in the patient.

54. The method of claim 41, wherein the patient is free of Alzheimer's disease.

55. The method of claim 54, wherein the patient is free of Alzheimer's disease and has no risk factors thereof.

71. A method of prophylactically treating a patient having a known genetic risk of Parkinson's disease, the method comprising

administering to the patient an effective regime of an agent that induces an immunogenic response against Aβ in the patient and thereby effecting prophylaxis of the disease;

wherein the agent is Aβ or an immunogenic fragment thereof, and the agent is linked to a carrier that helps elicit an immune response to the agent or is administered with an adjuvant that augments an immune response to the agent, or is an antibody to Aβ.

72. The method of claim 71, wherein the agent is Aβ or an immunogenic fragment thereof.

73. The method of claim 71, wherein the agent is an antibody to Aβ.

74. A method of prophylactically treating a patient having a known genetic risk of Parkinson's disease, comprising

administering to the patient an effective regime of an agent that induces an immunogenic response against alpha-synuclein and an agent that induces an immunogenic response against Aβ in the patient and thereby effecting prophylaxis of the disease;

wherein the agent that induces an immunogenic response against alpha-synuclein is alpha synuclein or an immunogenic fragment thereof and the agent is linked to a carrier that helps elicit an immune response to the agent or is administered with an adjuvant that augments an immune response to the agent, or an antibody to alpha synuclein, and the agent that induces an immunogenic response against Aβ is Aβ or an immunogenic fragment thereof and the agent is linked to a carrier that helps elicit an immune response to the agent or is administered with an adjuvant that augments an immune response to the agent, or an antibody to Aβ.

75. The method of claim 71, wherein the agent is administered peripherally.

76. The method of claim 71, wherein the effective regime comprises administering multiple dosages over a period of at least six months.

79. The method of claim 71, wherein the patient is free of Alzheimer's disease.

80. The method of claim 79, wherein the patient is free of Alzheimer's disease and has no risk factors thereof.

81. The method of claim 41, wherein the patient is free of clinical symptoms of a disease characterized by extracellular amyloid deposits.

82. The method of claim 45, wherein the patient is free of clinical symptoms of a disease characterized by extracellular amyloid deposits.

83. The method of claim 71, wherein the patient is free of clinical symptoms of a disease characterized by extracellular amyloid deposits.

84. The method of claim 74, wherein the patient is free of clinical symptoms of a disease characterized by extracellular amyloid deposits.

10. EVIDENCE APPENDIX

US 6,787,144 (reference #C cited by Examiner on PTO-892, April 7, 2005).

11. RELATED PROCEEDINGS APPENDIX

A copy of a Board decision in a related application, US Application No. 09/723,765 is attached.

The opinion in support of the decision being entered today was *not* written for publication and is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DALE B. SCHENK

Appeal 2006-3375
Application 09/723,765
Technology Center 1600

ON BRIEF

Before SCHEINER, GRIMES, and LINCK, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating or preventing Alzheimer's disease. The Examiner has rejected the claims for obviousness-type double patenting, indefiniteness, and nonenablement. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the rejections for obviousness-type double patenting but reverse the rejections for indefiniteness and nonenablement.

BACKGROUND

Alzheimer's disease is characterized by lesions in the brain known as senile plaques. (Specification 1.) "The principal constituent of the plaques is a peptide termed Aβ or β-amyloid peptide. Aβ is an internal fragment of 39-43 amino acids of a precursor protein termed amyloid precursor protein (APP)." (*Id.*)

The specification discloses "methods of preventing or treating a disease associated with amyloid deposits of Aβ in the brain of [a] patient. For example, the methods can be used to treat Alzheimer's disease. . . . Such methods entail administering fragments of Aβ or analogs thereof eliciting an immunogenic response against certain epitopes within Aβ." (Specification 4.)

DISCUSSION

1. CLAIMS

Claims 1, 14, 36, and 40-42 are pending and on appeal. Claims 1 and 36 are representative and read as follows:

1. A method of treating a patient having Alzheimer's disease, comprising administering to the patient an effective dosage to treat the disease of an N-terminal segment of Aβ (SEQ ID NO:42) consisting of residues beginning at residue 1 of Aβ and ending at residues 7-11 of Aβ and the segment being linked to a carrier molecule to form a conjugate, wherein the carrier molecule helps elicit an immune response to the N-terminal segment, and wherein if the carrier molecule is a polypeptide the polypeptide is heterologous to Aβ.

36. A method of prophylaxis of Alzheimer's disease in a patient at risk of the disease, comprising administering to the patient an effective dosage to effect prophylaxis of the disease of an N-terminal segment of Aβ (SEQ ID NO:42), the segment consisting of residues beginning at residue 1 of Aβ and ending at residues 7-11 of Aβ and the segment being linked to a carrier molecule to form a conjugate, wherein the carrier molecule helps elicit

an immune response to the N-terminal segment, and wherein if the carrier molecule is a polypeptide the polypeptide is heterologous to Aβ.

Thus, claims 1 and 36 are respectively directed to methods of treating and preventing Alzheimer's disease by administering a conjugate containing one of five fragments of Aβ: N-terminal amino acid residues 1-7, 1-8, 1-9, 1-10 or 1-11. The Aβ fragment is linked to a carrier molecule that is different from Aβ and that "helps elicit an immune response to the N-terminal segment."

2. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 14, 36, and 40-42 stand rejected under the judicially created doctrine of obviousness-type double patenting as follows:

• Claims 1, 36, 41, and 42 as not patentably distinct from claims 59-104 of application 09/724,940 (now U.S. Patent 6,905,686);

• Claims 1, 14, 36, and 40-42 as not patentably distinct from claims 58, 65, 76, 78, 83, 88, 90, 99, 101, 106, 111, 113, 118, and 119 of application 09/724,567 (now U.S. Patent 6,890,535); and

• Claims 1, 14, 36, and 40-42 as not patentably distinct from claims 11, 59, 76, 88, 99, 106, and 111 of application 09/724,953 (now U.S. Patent 6,875,434).

Appellant's brief does not argue that the rejections are improper but indicates that "Appellant is prepared to file a terminal disclaimer" to overcome the rejections. (Br. 4-5.) Since Appellant has not provided any basis on which to conclude that the rejections are improper, we affirm them.

3. DEFINITENESS

Claims 1, 14, 36, and 40-42 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner argues that

> the phrase 'an effective amount' is indefinite in that the claims fail to state the function to be achieved. More than one effect is implied via the specification and/or relevant art. For example the treating may require antibody production, amyloid plaque clearance, enhanced performance in cognitive function or other such symptom of a disease associated with amyloid deposi[t] of Abeta in the brain of a patient.

(Answer 19.)

Appellant argues that "the claims do indeed state the function to be achieved, that is, the dosage is effective to treat (claim 1) or effect prophylaxis (claim 36) of Alzheimer's disease." (Br. 17.) Appellant points to page 36 of the specification for definitions of treating and prophylaxis. (*Id.*)

We will reverse this rejection. As Appellant notes, the specification expressly defines the terms "therapeutically- or prophylactically-effective dose." (Specification 36, ll. 14-27). The specification defines a prophylactically effective dose as

> an amount sufficient to eliminate or reduce the risk, lessen the severity, or delay the outset of the disease, including biochemical, histologic and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of [Alzheimer's] disease.

(*Id.*, ll. 14-19.) The specification defines a therapeutically effective dose as

> an amount sufficient to cure, or at least partially arrest the symptoms of the disease (biochemical, histological and/or

> behavioral), including its complications and intermediate pathological phenotypes in development of the disease.

(*Id.*, ll. 19-23.)

Thus, when the claims are read in light of the specification, the skilled artisan would understand that the "effective dosage" recited in claims 1 and 36 means a dosage that results in at least one of the effects recited in the specification. That is, a prophylactically effective dosage would be understood to mean a dosage that reduces the likelihood of developing, lessens the severity of, or delays the onset of any of the symptoms of Alzheimer's disease, and a therapeutically effective amount would be understood to mean an amount that at least partially arrests any of the symptoms of Alzheimer's disease.

These definitions may be broad but they are not indefinite. *See In re Miller*, 441 F.2d 689, 693, 169 USPQ 597, 600 (CCPA 1971) ("[B]readth is not to be equated with indefiniteness."). We therefore reverse the rejection under 35 U.S.C. § 112, second paragraph.

4. ENABLEMENT

Claims 1, 14, 36, and 40-42 stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled. The Examiner argues that the specification does not enable the full scope of the claims, although she concedes that it is enabling for treating "PDAPP transgenic mice which over-express amyloid by administration of AN1792 (human Abeta1-42), rodent Abeta1-42, Abeta1-5 conjugated to sheep anti-mouse IgG, and Aβ1-7 in tetrameric MAP configuration as exemplified . . . [in] the specification." (Answer 7.)

PDAPP mice "exhibit Alzheimer's type overproduction and build up of beta-amyloid within the brain" and the Examiner acknowledges that the "specification teaches that the administration of particular polypeptides is able to reduce beta-amyloid within the brains" of such mice. (*Id.* at 8.) The Examiner also cites several references that "teach effective treatment of Alzheimer's disease and cognition deficits associated with amyloid plaque deposits upon beta-amyloid administration of beta-amyloid 1-28 administration." (*Id.* at 10.)

The Examiner concludes, however, that this guidance is insufficient to enable the claims. The Examiner argues that while PDAPP mice are "an art accepted animal model of Alzheimer's disease" (*id.* at 24), they do not exhibit all the characteristics of Alzheimer's disease in humans, such as paired helical filaments. (*Id.* at 13.) The Examiner also points out that the working examples in the specification include just one peptide within the scope of the present claims. (*Id.* at 14-15). The Examiner discounts the references showing removal of amyloid plaque on the basis that the "references do not teach . . . the regions or epitopes within beta-amyloid 1-42 or 1-28 peptides which are responsible for mediating plaque removal or the beneficial effects." (*Id.* at 10.)

The Examiner argues that the "specification fails to establish the structure that is required for the claimed biological activity in prophylaxis or treatment of Alzheimer's disease, and the model system is not established as predictive." (*Id.* at 14.) Thus, she concludes,

> a substantial amount of experimental trial and error [would be required] to produce a peptide of the claimed formula that also retains the biological activities recited in the claims. This trial

> and error would clearly constitute undue experimentation and, therefore, the instant specification is not enabling for the full scope of the peptides as claimed.

(*Id.*)

Appellant argues that "only five Aβ peptides (Aβ1-7, 1-8, 1-9, 1-10, and 1-11) are included in the claims." (Br. 7.) Appellant argues that making and testing these five peptides would not require a great quantity of experimentation; that the specification provides considerable guidance; that the "state of the art is advanced in that the claimed peptide conjugate can be made by standard methodology, and tested using an art-recognized transgenic mouse model"; and that the skill in the art is high. (*Id.*) Appellant concludes that when the *Wands* factors are correctly analyzed, the Examiner has not shown that the claims are nonenabled. (*Id.*)

We agree with Appellant that the Examiner has not shown that practicing the claimed method would require undue experimentation. The claims on appeal are very narrow: they require administering a conjugate that comprises one of only five fragments of Aβ. We do not agree with the Examiner's interpretation of the claims as "encompass[ing] a multitude of analogs or equivalents" (Answer 12). The claims specify "an N-terminal segment of Aβ (SEQ ID NO:42) consisting of residues beginning at residue 1 of Aβ and ending at residues 7-11 of Aβ." Thus, the claims are limited to conjugates that include an Aβ peptide consisting of the first 7, 8, 9, 10, or 11 amino acids in SEQ ID NO:42.

These peptides can be conjugated to any "carrier molecule [that] helps elicit an immune response to the N-terminal segment," other than Aβ itself, but the Examiner has not established, or even argued, that the carrier

molecule part of the conjugate would be a source of significant experimentation. Thus, for purposes of the enablement analysis, the claims are limited to methods of administering only five specific peptides.

The specification provides a working example that describes the administration of full-length Aβ (Aβ 1-42) to mice that overexpress "APP with a mutation . . . that predisposes them to develop Alzheimer's-like neuropathology." Page 47. The Examiner states that the PDAPP mouse "is an art-accepted animal model of Alzheimer's disease." (Answer 24.)

The specification states that mice treated with Aβ 1-42 had either no amyloid plaques or greatly reduced amyloid plaques in their brains, in contrast to control mice, which "contained numerous amyloid deposits." Page 49, lines 9-11. The specification concludes that "Aβ1-42 injections are highly effective in the prevention of deposition or clearance of human Aβ from brain tissue, and elimination of subsequent neuronal and inflammatory degenerative changes." Page 51, lines 2-4.

The specification describes a second experiment in which Aβ 1-42 (a.k.a. AN1792) was administered to PDAPP mice "at a time point when amyloid plaques [were] already present in the brains." Page 52, lines 22-23. The results of the experiment are said to "show that AN1792 immunization of PDAPP mice possessing existing amyloid deposits slows and prevents progressive amyloid deposition and retard[s] consequential neuropathologic changes in the aged PDAPP mouse brain." Page 60, lines 3-5.

The specification also describes an experiment in which various Aβ fragments were conjugated to a sheep antibody and their effects were compared to Aβ 1-42. Pages 60-68. The specification reports that the Aβ 1-5

conjugate brought about significant reductions in Aβ and Aβ 1-42 levels in cortex but no reduction was reported for Aβ levels in hippocampus or cerebellum; the other Aβ conjugates tested (1-12, 13-28, and 32-42, all conjugated to the same sheep antibody) were found to be ineffective in reducing Aβ levels. Page 64, line 30 to page 65, line 2.

The specification also reports the results of administering an Aβ conjugate as recited in the claims. The conjugate is described as a "multi-antigenic peptide" (MAP) in tetrameric configuration, and comprised the Aβ 1-7 peptide fused to a tetanus toxoid T-cell epitope. Page 99, line 25 to page 100, line 5. The specification reports that "the Aβ 1-7 MAP immunogen is effective in inducing a sufficient immune response significantly to retard Aβ deposition in the cortex." Page 101, lines 5-6.

Finally, the specification describes an experiment in which Aβ 1-42 was administered to monkeys and the reactivities of the resulting antibodies were mapped using fragments of Aβ. The specification reports that "in all cases the reactivity to the N-terminal peptide sequence was the predominant one." Page 104, lines 3-4. The most common additional reactivity is said to be centered around the N-terminal 10 amino acids; i.e., binding "directed to peptides covering amino acids -1–8, -1–9, and 2-11 of the AN1792 peptide. These reactivities, combined with that of the 1-10 peptide, represent the overwhelming majority of reactivity in all animals." Page 104, lines 7-9.

In our view, the working examples in the specification provide significant guidance to those of skill in the art. The working examples show *in vivo* results using an art-accepted model, they show that one peptide conjugate like that defined in the instant claims produces results similar to the

full length Aβ peptide, and they show that results produced by the full-length peptide reasonably appear to be due to an epitope in the N-terminal eleven amino acids of Aβ. We agree with Appellant that the evidence does not support the Examiner's position that undue experimentation would be required to practice the claimed methods.

As we understand it, the Examiner has two objections to the specification's working examples. First, the Examiner acknowledges that PDAPP mice are an art-accepted animal model for Alzheimer's disease, but she asserts that they are not "predictive of the results that would be expected" in humans because PDAPP mice lack some of the histological features of Alzheimer's disease, including "paired helical filaments." Examiner's Answer, page 9.

We do not agree with the Examiner that the differences between PDAPP mice and human Alzheimer's disease patients would lead those skilled in the art to doubt the predictive value of the specification's working examples. The prior art of record demonstrates that those skilled in the art accepted PDAPP mice as a useful model for testing drugs for treating Alzheimer's disease. Games[1] states that the PDAPP mouse "offers a means to test whether compounds that lower Aβ production and/or reduce its neurotoxicity *in vitro* can produce beneficial effects in an animal model prior

[1] Games et al., "Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein," *Nature*, Vol. 373, pp. 523-527 (1995).

to advancing such drugs into human trials." Page 527. Similarly, Chen[2] states that PDAPP mice "provid[e] an useful animal model for the testing of various therapeutic interventions directed toward specific aspects of the neurodegenerative process." Page 333.

The evidence shows that those skilled in the art considered PDAPP mice to be a useful animal model for testing drugs intended to treat the symptoms of Alzheimer's disease; to be useful, an animal model must provide results that are reasonably predictive of those expected in humans. Certainly, there is no guarantee that the results seen in mice will hold for humans, but enablement does not require absolute predictability. *See In re Brana*, 51 F.3d 1560,1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995): "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." (Although the *Brana* court referred to "usefulness," the rejection on appeal was for lack of enablement. *See id.* at 1568, 34 USPQ2d at 1442.)

A method of treatment can be enabled even if it has not been shown to be, and even if it never turns out to be, clinically useful. "'[O]ne who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.'" *Brana*, 51 F.3d at

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[2] Chen et al., "Neurodegenerative Alzheimer-like pathology in PDAPP 717V→F transgenic mice," *Progress in Brain Research*, Vol. 117, pp. 327-333 (1998).

1567, 34 USPQ2d at 1442 (quoting *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961)). If those skilled in the art would reasonably expect the claimed method to produce a therapeutic effect, it can be enabled even if it has not (yet) been shown to be safe and effective in clinical trials.

The Examiner's second objection to the working examples, as we understand it, is that only one peptide within the scope of the instant claims was shown to be effective in PDAPP mice:

> There is only a single conjugate peptide amongst those claimed that is disclosed as exhibiting positive effects in the model system and that is the Aβ1-7 peptide in MAP configuration. . . . The claims are directed to a broader range of peptides. Yet no predictability is established for expecting similar function from these constructs when only a single member of the genus was effective and even[ ] then was only effective for lowering cortical Aβ levels.

Examiner's Answer, pages 14-15.

Again, we do not share the Examiner's concern. The specification shows that Aβ 1-42, Aβ 1-5 conjugated to a sheep antibody, and Aβ 1-7 conjugated to a tetanus toxoid peptide all had similar *in vivo* effects when administered to PDAPP mice. The specification also shows that the "overwhelming majority of [antigenic] reactivity in all animals" was centered around the N-terminal ten amino acids of Aβ; i.e., from amino acid -1 to amino acid 11.

In our view, the evidence of record is sufficient to lead those skilled in the art to expect that Aβ peptides 1-8, 1-9, 1-10, and 1-11 would have effects similar to Aβ 1-7 peptide when conjugated to a carrier molecule and administered to a patient.

SUMMARY

We affirm the rejections for obviousness-type double patenting. However, we reverse the rejection for indefiniteness because the specification defines what is meant by an "effective amount." We also reverse the rejection for nonenablement because the Examiner has not adequately shown that practicing the claimed methods would have required undue experimentation.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a)(1)(iv) (2006).

AFFIRMED

Toni R. Scheiner)
Administrative Patent Judge)
)
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